UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/822,033	03/24/97	MARASCO	W 13471-FWC

18N2/1001

DAVID G CONLIN
DIKE BRONSTEIN ROBERTS & CUSHMAN
130 WATER STREET
BOSTON MA 02109

EXAMINER	
CAMPELL, B	
ART UNIT	PAPER NUMBER
1819	19

DATE MAILED: 10/01/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1, 3-16 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1, 3-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

The amendments filed 9/23/96 (in the parent application) and March 24, 1997 have been entered.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5 and 7-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al. Beug et al. disclose a nucleic acid carrier, which is a fusion protein consisting of transferrin fused to a polycationic polypeptide, complexed with a nucleic acid molecule. Beug et al. also suggest the use of protamine as the nucleic acid binding moiety (p. 6) and demonstrate the use of the carrier to transform cells *in vitro* (examples 5-13). Beug et al. do not teach a carrier in which the targeting moiety is an antibody or the nucleic acid encodes *Pseudomonas* exotoxin A (PEA), nor do they demonstrate transformation of cells *in vivo*. Chaudhary et al. disclose a fusion protein which consists of a single chain antibody having a truncated form of PEA (containing domain III) fused to its carboxyl end (p. 1068). This fusion protein is used to deliver PEA specifically to cells expressing the surface antigen recognized by the antibody (entire document). Chaudhary et al. teach a method for cloning antibody genes (entire document), and a method for producing and purifying the fusion protein (p. 1067). Chaudhary et al. teach that the truncated form of PEA is a potent toxin and disclose a plasmid encoding the truncated PEA (p. 1066, Fig. 5). Chaudhary et al. teach that a fusion protein containing an antibody against the interleukin-2 receptor was used to selectively deliver PEA to cells expressing the receptor (p. 1066). Wu et al. teach a nucleic acid carrier consisting of a cell-receptor specific ligand

linked to a polycationic polypeptide (entire document), and demonstrate successful use of this carrier to deliver and express DNA to a specific cell type *in vivo* (by intravenous injection; col. 11). Wu et al. suggest that an antibody could be used as targeting moiety (col. 6, lines 3-7), that protamine could be used as the polycationic polypeptide (col. 4, lines 39-44), and that a peptide bond could be used to link the targeting and DNA binding moieties (col. 5, lines 45-48).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art to develop the claimed compositions and methods. It would have been obvious to modify the transferrin-polycationic polypeptide fusion of Beug et al. by substituting an antibody for transferrin, given the suggestion of Wu et al. to use an antibody for cell type-specific targeting of DNA and the demonstration of successful cell type targeting with antibodies by Chaudhary et al. It would have been obvious to use protamine as the DNA binding protein, given the suggestion to do so by Beug et al. and Wu et al. It would have been obvious to fuse the DNA binding protein to the carboxyl end of the antibody, since Chaudhary et al. had shown that this arrangement preserved the ability of the antibody to recognize antigen. Having made the antibody-polycationic polypeptide fusion protein by the methods of Chaudhary et al., it would have been obvious to use it to deliver polynucleotides *in vivo* as discussed by Beug et al. and demonstrated by Wu et al. using different targeting moieties. It would have been obvious to deliver a gene encoding PEA, since Chaudhary et al. had shown this toxin to be extremely potent. One would have been motivated to develop the claimed compositions and methods, given the knowledge that virtually any nucleic acid could be delivered in this manner, as taught by Beug et al., and that use of antibodies would allow targeting of any cell type which produces a cell type-specific antigen. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al. as applied to claims 1, 3-5 and 7-16 above, and further in view of Ryder et al. Beug et al. in view of Chaudhary et al. and Wu et al. teach fusion proteins, consisting of an

antibody fused to a DNA-binding protein, complexed with nucleic acids, as discussed above. Beug et al. in view of Chaudhary et al. and Wu et al. do not teach fusion proteins wherein the DNA-binding protein is one of those recited in claim 6. Ryder et al. disclose the amino acid sequences of the DNA-binding regions of three *jun* proteins (Fig. 2) and the nucleotide sequence of *jun-D* cDNA (Fig. 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize one of the *jun* sequences disclosed by Ryder et al. as the DNA-binding moiety of the fusion protein of Beug et al. in view of Chaudhary et al. and Wu et al. One would have expected the *jun* protein to be effective, since it was known to bind certain DNA sequences. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In the response of September 23, 1996, Applicants argue that the references must be read in their entirety, not selectively, and that the references mostly discuss methods and compositions other than those claimed. This argument is not persuasive. There is no requirement that references must "mostly" discuss the subject matter for they are relied upon as prior art. Discussion of other compositions and methods does not constitute "teaching away" from compositions and methods which are discussed to a lesser extent. Furthermore, if one were to disregard the "minor" parts of a reference, would that not be a selective reading of the reference, which is not allowed?

Applicants argue that Chaudhary et al. adds nothing to the combination of Beug et al. and Wu et al. This argument is not persuasive because Chaudhary et al. show that an antibody can be used as a targeting ligand to direct a macromolecule to a desired cell type. Thus, while Wu et al. suggest using an antibody as targeting ligand, Chaudhary et al. provide a reasonable expectation of success. Furthermore, Chaudhary et al. show how to make a fusion protein combining the antibody and another molecule while maintaining target specificity.

No claim is allowed.

This is a file wrapper continuation of applicant's earlier Application No. 08/199,070. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected

on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1800 are 703-305-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell
September 30, 1997

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800